Idiopathic central diabetes insipidus presenting in a very low birth weight infant successfully managed with lyophilized sublingual desmopressin

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Received: 22 April 2014, Revised: 26 June 2014, Accepted: 8 September 2014

SUMMARY: Hanta D, Törer B, Temiz F, Kılıçdağ H, Gökçe M, Erdoğan Ö. Idiopathic central diabetes insipidus presenting in a very low birth weight infant successfully managed with lyophilized sublingual desmopressin. Turk J Pediatr 2015; 57: 90-93.

Neonatal central diabetes insipidus (DI) is an extremely rare disorder that can cause severe morbidity and mortality. We have reported a very low birth weight infant with idiopathic central DI presenting in the first month of life who was successfully treated with sublingual desmopressin therapy. In this report, we emphasize that central DI should be kept in mind in an infant with unexplained hypernatremia and polyuria. Timely diagnosis and treatment with lyophilized desmopressin may prevent severe morbidity and mortality.

Key words: central diabetes insipidus, premature infant, desmopressin therapy, hypernatremia, polyuria.

Neonatal central diabetes insipidus (DI) is an extremely rare disorder that can cause severe morbidity and mortality[1]. Although the etiology of and management options for central diabetes insipidus in the neonatal period are not clearly documented, early diagnosis and therapy with desmopressin may prevent severe morbidity[2]. In this paper, we report a very low birth weight infant with idiopathic central DI presenting in the first month of life who was successfully treated with sublingual desmopressin therapy.

Case Report

An 1100 g infant girl was born to a 31-year-old mother at 28 weeks of gestation after a pregnancy complicated by premature labor. She was third child of nonconsanguineous healthy parents. There was no family history of DI, nor were there other hereditary disorders. The patient was intubated and given surfactant therapy immediately after birth. Apgar scores were 5 and 7 at the first and fifth minute, respectively. Her clinical course was complicated by respiratory distress syndrome, requiring mechanical ventilation for one day. After extubation, continuous oxygen supplementation through a nasal CPAP/nasal cannula was administrated for the next 5 days. Ampicillin and amikacin were also administrated for the first 7 days of life for early onset sepsis without central nervous system involvement. Serial cranial ultrasound scans were normal on day 2, 14, 30 and 50. She was noted to be hypernatremic (highest serum [Na^+], 160 mEq/L) after the third day of life. Highest urine output was 3 ml/kg per hour, and postnatal weight loss was 15% of birth weight. These results, both the weight loss and the rise in serum sodium concentration ([Na^+]), were attributed to transepidermal free water loss. Hypernatremia was resolved by increasing fluid intake and by the removal of sodium from parenteral nutrition. However, significant hypernatremia and polyuria recurred on day 11 and persisted despite elevating fluid intake up to 220 ml/kg/day and decreasing Na+ intake to 2 mEq/kg/day over the next several days (highest serum [Na^+], 170 mEq/L; highest urine output, 6.5 ml/kg/h). Serum and urine osmolality

were 362 mOsm/kg and 165 mOsm/kg, urine sodium was 15 mEq/dl, urine specific gravity was 1010. No glucose was detected in the urine analysis. Laboratory findings, including blood urea nitrogen, creatinine, potassium, calcium and bicarbonate, were normal, without evidence of renal dysfunction or metabolic acidosis. No hypokalemia was noted, and serum [Ca^{+2}] ranged between 8.7 and 10 mg/dl. Plasma concentrations of cortisol, thyroxine and thyroid-stimulating hormone were within normal limits, and renal/bladder ultrasound scans were normal [cortisol:7 μg/dl (2.3-19.4); free T_4:1.04 ng/dl (0.7-3); TSH:1.52 μIU/ml (0.3-6.5)]. Serological tests for *Toxoplasma gondii*, cytomegalovirus (CMV), rubella virus and herpes simplex virus type 1 and type 2 were negative. Cranial and hypophysis magnetic resonance imaging were normal (however, the scan was performed without gadolinium) (Figure 1a, b, c). The cerebral hemispheres, corpus callosum and cerebellum looked normal. Hypothalamic-pituitary magnetic resonance imaging to identify hyperintensities in the posterior pituitary (posterior pituitary bright spot on midsagittal T1-weighted MR) or thickening of the pituitary stalk were normal. Clinical and laboratory findings were consistent with DI. For further diagnostic and therapeutic purposes, sublingual desmopressin therapy was started on day 20, at a dose of 3 to 4 μg/day divided every 12 hours, which resulted in normalization of serum [Na^+] and urine output. Serum sodium levels ranged between 135 and 146 mEq/L, and urine output decreased to 3 ml/kg per hour. The infant manifested good weight gain on full enteral feeding of preterm formula at 150 ml/kg per day. She was discharged home on day 52 with normal serum [Na^+], and with sublingual desmopressin therapy maintained at a dose of 1–2 μg/day divided every 12 hours.

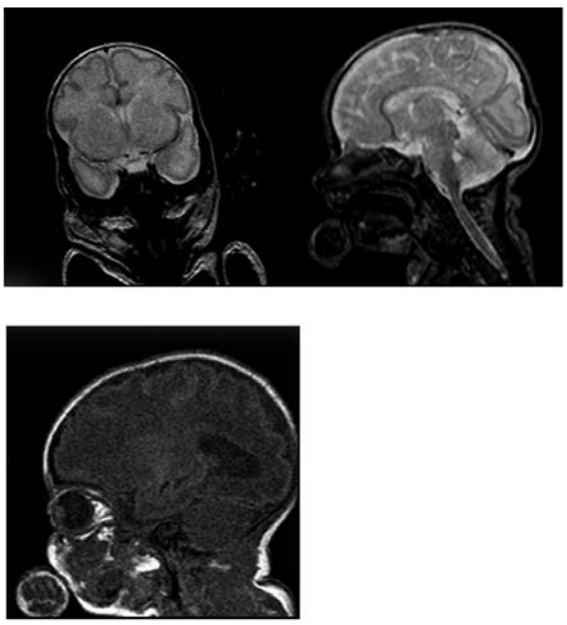

Fig. 1. Cranial and hypophysis-hypothalamic magnetic resonance imaging was normal (a: coronal T2, b: sagittal T1, c: sagittal T2).

Discussion

Although the etiology and treatment of central DI has been well described previously in several case series in children, it is rarely reported in the neonatal population, especially in very low birth weight (VLBW) premature infants[1,3]. The most prevalent cause of central DI among infants and children is intracranial tumors. Central DI in VLBW preterm infants as a consequence of intraventricular hemorrhage is rarely reported[2]. Central DI has been reported in neonates secondary to intraventricular hemorrhage, group B streptococcal meningitis, septo-optic dysplasia, *Listeria monocytogenes* sepsis, congenital cytomegalovirus and midline intracranial defects, and following surgical resection of a suprasellar mass[3]. The prevalance of idiopathic central DI is less than 15%[3].

Establishing the diagnosis in neonates is challenging because of ''naturally'' occurring significant changes in total body fluid and electrolyte balance upon transition to life ex utero. Unresponsive, persisting polyuria and hypernatremia, however, should raise the suspicion of DI, especially in the presence of intraventricular hemorrhage. Persistent hypernatremia, detected from the beginning of the first week of life in our patient, was initially thought to be due primarily to transepidermal loss of fluid. However, as persistent hypernatremia and polyuria continued in the follow-up period, DI was implicated.

In the neonatal literature, there are several previous case reports of infants presenting with DI in the first month of life. Yarber and Wood[4] reported a 1040 g infant boy delivered at 28 weeks of gestation, who developed

unexplained hypernatremia and polyuria within the first week of life and was subsequently diagnosed as idiopathic central DI. He was initially treated with subcutaneous dDAVP. Therapy was changed to oral dDAVP before discharge to home. Molnar Z et al.[5] reported a male infant born at 28 weeks and 2 days of gestation with a birth weight of 1300 g who developed hypernatremia in the second week of life as a result of transient central DI. Cranial ultrasound on day 1 revealed a large intraventricular hemorrhage with parenchymal involvement on the left side. He was treated with oral desmopressin. Random cortisol levels obtained on two occasions, along with ACTH, GH, TSH and free T4, were all found to be normal. The thyroid function tests and serum cortisol level of our patient were normal. There was no evidence of any coexisting endocrinopathy. Weight and height velocities were age appropriate after sublingual desmopressin treatment. Magnetic resonance imaging did not show any abnormalities of the hypothalamic-pituitary axis. Serology was negative for congenital CMV. Neither bacterial sepsis nor meningitis was documented during the hospital stay. Thus, our patient was considered as idiopathic central DI.

In a review of the literature, treatment of central DI has initially been conducted by administering intramuscular pitressin in tannate oil[6]. Lysine vasopressin is another synthetic peptide that has been used in both intravenous and intranasal forms. Pitressin and vasopressin act on both the V_1 and V_2 receptors, causing them to have more pronounced pressor effects as well as potentially significant gastrointestinal side effects[7]. In the late 1960s, the vasopressin analog desmopressin was developed. It is available in oral, intravenous and intranasal forms and has become the treatment of choice for patients with central DI. It appears to act almost exclusively on the V_2 receptor and has minimal pressor effects.

Management of central DI in neonates is challenging[5]. Although intranasal desmopressin use in children is well documented, there is some controversy regarding the method of delivery of desmopressin in neonates for long-term therapy. Paulsen-Fjellestad et al.[8] noted that nasal absorption is irregular in infants, leading to hypernatremia and wide fluctuations in antidiuretic effects. Stick et al.[9] reported the use of intranasal dDAVP therapy in a term infant with a cleft lip and palate; however, therapy was changed to oral dDAVP due to significant variability in urine output and weight gain. Ozaydın et al.[10] reported a female infant with facial abnormalities including a bilateral cleft lip and palate, ectrodactyly and central DI. She had a history of recurrent hypernatremic attacks and was treated successfully with oral desmopressin. Atasay et al.[11] investigated the effect of oral administration of desmopressin solution in a very low birth weight premature infant with central DI associated with grade 4 germinal matrix hemorrhage. They suggested that long-term successful management resulting in favorable growth and development during infancy can be achieved by using the oral route as an alternative to the nasal route. Quetin et al.[12], noting that idiopathic central DI is extremely rare during the neonatal period, reported a very low birth weight infant with idiopathic central DI who was successfully treated with oral desmopressin during the first month of life. We also treated our patient with sublingual desmopressin. Initially, sublingual lyophilized desmopressin (a 60-microgram lyophilized tablet is equivalent to 0.1 mg desmopressin) was administered at a dosage of 3-4 mg twice a day (2.5 μg/kg/day); the dosage was reduced to 1-2 mg twice a day once a clinical response was established. In one study, desmopressin was commenced upon diagnosis of central DI, with a median initial dose of 2 μg/kg/day (0.26-18.5)[13]. Ozaydın et al.[10] and Atasay et al.[11] used oral desmopressin at a dosage of 2.5 μg/kg/day. However, management of central DI in this age group poses a special set of problems owing to the obligate high water intake in milk-based formulas[13]. Due to the risk of hyponatremia in long-term anti-diuretic hormone therapy, these babies should be managed on a high volume of formula with a low renal solute load. Despite these considerations, we achieved normal urine output and serum sodium levels without provoking significant iatrogenic hyponatremia by administering low-dose desmopressin sublingually.

In conclusion, we have reported a very low birth weight premature infant with idiopathic central DI presenting in the first few weeks. She was successfully treated with sublingual lyophilized

desmopressin. In this report, we emphasize that central DI should be kept in mind in an infant with unexplained hypernatremia and polyuria. Timely diagnosis and treatment with desmopressin may prevent severe morbidity and mortality.

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